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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,853	03/22/2004	Pramod B. Mahajan	1410	4376

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EXAMINER	
KRUSE, DAVID H	
ART UNIT	**PAPER NUMBER**
1638	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/18/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,853	MAHAJAN ET AL.	
	Examiner	Art Unit	
	David H. Kruse	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *8-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-7, in the reply filed on 6 October 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 8-20 are withdrawn from further consideration pursuant to 37 CFR § 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6 October 2006.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR § 1.48(b) and by the fee required under 37 CFR § 1.17(i).

Specification

4. The disclosure is objected to because of the following informalities: At page 1, first line, "priority to" should read -- benefit of -- when referring to a provisional application.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-7 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim a method of reducing expression of a target polynucleotide in a plant cell by targeted gene modification to produce an active RDS element within the targeted polynucleotide, wherein expression of the target polynucleotide is reduced. Applicants also claim said method wherein the targeted gene modification is performed by a site-specific recombination method. Applicant defines an active RDS element as being "As used herein a "RNA destabilizing sequence element" or "RDS element" refers to a polynucleotide containing sequences ATAGAT and GTA, which are capable of destabilizing RNA. In addition, a third domain may be included that contains the sequence GGA. The three domains can be placed in the following 5' to 3' order of: GGA, followed by ATAGAT, followed by GTA." on page 3 of the specification.

Applicants teach a maize phytoene synthase gene of maize that may be modified to contain an RDS element on page 25 of the specification and a maize herbicide safener-binding gene that may be modified to contain an RDS element on page 29 of the specification.

Applicant does not actually teach use of the claimed method to modify a target polynucleotide to produce an RDS element wherein expression of the target polynucleotide is reduced. The specification only states prophetically that "The effect of this genomic modification on the stability of phytoene synthase mRNA will be confirmed by evaluation of the steady-state levels of phytoene synthase mRNA in the transformants using RT-PCR" on page 27 of the specification.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The breadth of the claims are directed to produce an "active" RDS element anywhere within a targeted polynucleotide; Applicants state that "These elements may

be found or introduced into any part of a gene including, but not limited to, the 5' untranslated region, the 3' untranslated region, the coding region, an intron, an exon, secretory regions or any other part of the nucleotide that is transcribed into RNA" (page 3, lines 24-27 of the specification). Applicants state that the RDS element can be at essentially any distance from either the poly A tail to the start of transcription or from the start of transcription in the paragraph spanning pages 3-4 of the specification. Applicants state that the ATAGAT and GTA sequences could be 1 to 50, 1 to 75 or 1-100 base pairs apart (page 4, 2nd paragraph of the Remarks).

Applicants cite the teachings of Newman *et al* 1993, The Plant Cell 5: 701-714, herein made of record. Newman 1993 teaches that naturally occurring RDS elements occur anywhere from 19 to 83 nucleotide downstream from the mRNA stop codon, and that there is approximately 12 nucleotides between the ATAGATT and the GTA sequence (see Figure 1 on page 702). Applicants teach a maize phytoene synthase gene of maize that may be modified to contain an RDS element on page 25 of the specification and a maize herbicide safener-binding gene that may be modified to contain an RDS element on page 29 of the specification. The phytoene synthase gene of maize taught by Applicants has 19 nucleotides between the ATAGATT and the GTA sequence (see SEQ ID NO: 1) and the maize herbicide safener-binding gene taught by Applicants has 15 nucleotides between the ATAGATT and the GTA sequence (see SEQ ID NO: 6). Hence, it is unclear if the maize sequences taught by Applicants would produce a destabilized mRNA product. In addition, Applicants assert that an RDS element can be inserted anywhere into a target polynucleotide to produce reduced

expression, this assertion is contradictory to the teachings of the art, especially the 5' untranslated region or an intron as stated on page 3, lines 24-27 of the specification.

At page 25, lines 4-17 of the specification, Applicants teach changing a GTC sequence to GAC, but this is not a GTA sequence that Applicant asserts is required to produce a RDS element in a target polynucleotide. At page 29, lines 5-18 of the specification, Applicants teach changing a TGTATG sequence to TGTATC, but this is not directed to producing a GTA sequence that Applicant asserts is required to produce a RDS element in a target polynucleotide. Neither teaching is directed to producing a GTA sequence that follows an ATAGAT sequence, in fact giving the teachings of the art it is unclear what Applicants guidance is directed to.

Newman 1993 teach that to achieve a marked destabilization of a heterologous mRNA (a mRNA that does not naturally contain an RDS element), that multiple copies are required, and that it is not unusual to find that multiple copies of a single regulatory element are necessary for maximal function in a foreign or altered context (page 709, right column, 2nd paragraph). Newman 1993 also teach that the DST sequences (syn. for RDS element as used by Applicants) were inserted ~250 bp upstream of the poly(a) addition site to avoid disrupting polyadenlyation (page 709, right column, 2nd paragraph). Applicants' specification is silent about what appears to be critical features required to practice the claimed invention within its full breadth. Hence, one of skill in the art at the time of Applicant's invention could not predictably produce a destabilized RNA using a single RDS element in a heterologous gene.

The preceding arguments are directed to enablement of the claimed method in general. The following is directed to enablement of the claims as they are directed to a method of targeted gene modification performed by a method using a site-specific recombination method as recited in instant claim 3 or the use of a recombinagenic oligonucleotide.

As stated above, all of Applicants' examples are prophetic, and do not appear to be directed to producing the specific RDS element required to practice the claimed invention. The use of site-specific recombination methods in plants, such as that taught by Baszcynski *et al* (U.S. Patent 5,929,301) or using a chimeric oligonucleotide as taught by Kmiec (U.S. Patent 5,565,350) were not predictable at the time of Applicants' invention (both references cited by Applicants). The method of Baszcynski *et al* requires insertion of a recombination site, which is typically done using methods that introduce recombination sites randomly into a plant's genome. Applicants provide no guidance on how to predictably target insertion of a recombination site into a target gene that would be required to practice the method of instant claim 3. The use of a chimeric oligonucleotide as taught by Kmiec in making targeted gene modifications *in vivo* in plants was not predictable at the time of Applicants' invention. The art teaches that often times the targeted nucleotide using a chimeric oligonucleotide as taught by Kmiec would produce nucleotide changes one or two bases upstream from the targeted nucleotide (Zhu *et al* 2000, Nature Biotechnology 18: 555-558; see Table 1 on page 556). The art teaches that in plants mixed base sequences other than the predicted nucleotide conversion have been observed, suggesting a plant-specific repair mechanism different

from the high-fidelity repair observed in the mammalian system and that this "unspecificity" has later been confirmed in an in vitro study using a tobacco cell-free extract (Anderson *et al* 2002, J Mol. Med. 80: 770-781; see page 772, right column, 2nd paragraph). Hence, given the breadth of the claims, the limited guidance by Applicants, the nature of the invention, the unpredictability of the art to which the instant claims are directed, the absence of a reduction to practice of the claimed method, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure it would have required undue trial and error experimentation by one of skill in the art at the time of Applicants' invention to use the invention as broadly claimed. This is particularly the issue as the art teaches that to achieve a marked destabilization of a heterologous mRNA (a mRNA that does not naturally contain an RDS element) that multiple copies are required and Applicants only provide guidance for introducing a single RDS element into a target polynucleotide in a plant.

7. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claim 3 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is indefinite because the claimed method fails to recite several critical steps, recognized in the art, that would be required to practice the claimed method, specifically introduction of a recombination site and the presence of a recombinase. Such omission amounting to a gap between the steps. See MPEP § 2172.01.

Claim Rejections - 35 USC § 102/103

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 2 and 4 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Sullivan *et al* 1996 (RNA 2: 308-315).

Applicants define targeted gene modification as follows on page 4, lines 19-21 of the specification; " As used herein, "targeted gene modification" refers to any process whereby a specific sequence modification is facilitated at a desired genetic locus by a transforming nucleic acid".

Sullivan *et al* disclose introducing a target polynucleotide being modified to produce an active RDS element and introduction of said target polynucleotide into a plant cell using both a β-globin and β-glucuronidase at page 309.

Sullivan *et al* do not specifically teach the method in a monocot plant cell.

At the time of Applicants' invention, introducing polynucleotides into monocot plant cells would have been considered by one of ordinary skill in the instant art as an obvious modification of the method of Sullivan *et al*, and it would have been obvious that one of ordinary skill in the art would have had a reasonable expectation of success.

Conclusion

12. No claims are allowed.

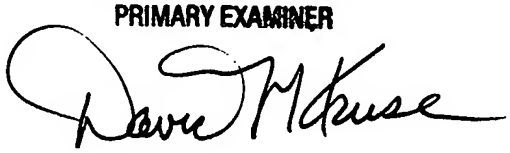
13. Claims 3 and 5-7 are free of the prior art, which neither discloses nor renders obvious the claims.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David H. Kruse, Ph.D. whose telephone number is (571) 272-0799. The examiner can normally be reached on Monday to Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached at (571) 272-0975. The central FAX number for official correspondence is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group Receptionist whose telephone number is (571) 272-1600.

DAVID H. KRUSE, PH.D.
PRIMARY EXAMINER



David H. Kruse, Ph.D.
11 December 2006

15. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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